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Non-Hodgkin lymphoma, body mass index and cytokine polymorphisms: a pooled analysis from the InterLymph consortium

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Abstract

Background—Excess adiposity has been associated with lymphomagenesis, possibly mediated by increased cytokine production causing a chronic inflammatory state. The relationship between obesity, cytokine polymorphisms and selected mature B-cell neoplasms is reported.

Method—Data on 4979 cases and 4752 controls from nine American/European studies from the InterLymph consortium (1988–2008) were pooled. For diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), joint associations of body mass index (from self-reported height and weight) and 12 polymorphisms in cytokines *IL1A* (rs1800587), *IL1B* (rs16944, rs1143627), *IL1RN* (rs454078), *IL2* (rs2069762), *IL6* (rs1800795, rs1800797), *IL10* (rs1800890, rs1800896), *TNF* (rs1800629), *LTA* (rs909253), and *CARD15* (rs2066847) were investigated using unconditional logistic

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regression. BMI-polymorphism interaction effects were estimated using the relative excess risk due to interaction (RERI).

Results—Obesity (BMI≥30kg m^{-2}) was associated with DLBCL risk (OR=1.33, 95%CI 1.02–1.73), as was *TNF-308GA+AA* (OR=1.24, 95%CI 1.07–1.44). Together, being obese and *TNF-308GA+AA* increased DLBCL risk almost two-fold relative to those of normal weight and *TNF-308GG* (OR=1.93 95%CI 1.27–2.94), with a RERI of 0.41 (95%CI −0.05,0.84, P(interaction)=0.13). For FL and CLL/SLL, no associations with obesity or *TNF-308GA+AA*, either singly or jointly, were observed. No evidence of interactions between obesity and the other polymorphisms were detected.

Conclusions—Our results suggest that cytokine polymorphisms do not generally interact with BMI to increase lymphoma risk but obesity and *TNF-308GA+AA* may interact to increase DLBCL risk.

Impact—Studies using better measures of adiposity are needed to further investigate the interactions between obesity and *TNF-308G>A* in the pathogenesis of lymphoma.

Keywords

Body mass index; genotype; polymorphism; non-Hodgkin lymphoma

Introduction

Immune dysregulation plays a pivotal role in lymphomagenesis, and epidemiological research has tended to concentrate on factors and exposures that interact with the immune system. In this regard obesity, which can cause a mild chronic inflammatory state, has been suggested to potentially increase the likelihood of lymphoid malignancy development. Earlier InterLymph pooled analyses reported that obesity was associated with an increased risk of diffuse large B-cell lymphoma (DLBCL) (1,2), and recent meta-analyses provide further support for this hypothesis (3,4).

Obesity-related inflammation is thought to result from the pro-inflammatory cytokines and chemokines that are produced by adipocytes and macrophages in adipose tissue (5). With weight gain, the numbers of adipocytes and macrophages increase as adipose tissue expands, increasing production of cytokines such as tumor necrosis factor-α (TNF), leptin, interleukin 1β (IL-1β) and IL-6, as well as chemokines and acute phase proteins (5). Ideally, to investigate whether increased levels of inflammation-related cytokines modulate the association between obesity and lymphoid neoplasms, serum levels of cytokines would be measured before cancer diagnosis. In the absence of such measurements, single nucleotide polymorphisms (SNPs) within genes that express cytokines may act as surrogates that indicate variation in risk of lymphoid neoplasms with obesity. Several putative functional SNPs in candidate cytokine genes were selected *a priori* by the InterLymph consortium due to their role in lymphoid development, and also- in the pro-/anti-inflammatory pathways which may be altered in the obese state. Among these cytokine SNPs, *TNF* (-308G>A, rs1800629), *LTA* (-252A>G, rs909253) and *IL10* (-3575T>A, rs1800890) have been associated with lymphoid neoplasms and DLBCL in particular (6–8). There has however been little exploration of the relationship between obesity and cytokines on the risk of these

malignancies (9–11). Here, we investigate gene-environment interactions between body mass index (BMI) and cytokine SNPs using data from case-control studies included in the International Lymphoma Epidemiology Consortium.

Materials and Methods

Data Sources

Through the InterLymph consortium, nine case-control studies conducted in the USA and five European countries between 1988 and 2008 that had individual level data on BMI and cytokine polymorphisms contributed to this pooled analysis. Data were provided via the InterLymph Data Coordinating Center (DCC) at the Mayo Clinic, Rochester, which was established in 2009 to centrally standardise and harmonise study data so that consistent datasets could be produced to expedite pooling projects. Descriptions of the included studies have been published (12–20); a brief outline is given in Table 1. Cases were ascertained using rapid identification techniques, and controls were randomly selected from population registers (6 studies), outpatient clinics (1 study) or hospital inpatients with non-neoplastic conditions (2 studies). Each study had the appropriate ethical committees' approval and participants gave their informed consent.

Diagnoses of lymphoid neoplasms were pathologically confirmed and coded to the World Health Organisation International Classification for Oncology Version 3 (ICDO3) (7 studies), REAL (Connecticut) and Working Formulation (UCSF) classifications. Diagnostic codes from the different schemas were bridged by the DCC using the same approach as in previous InterLymph analyses (21). The analysis here reports on specific lymphoid neoplasms: diffuse large B cell lymphoma (DLBCL: ICDO3 codes 9679, 9680, 9684), follicular lymphoma (FL: 9690, 9691, 9695, 9698), and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL: 9670, 9823) and all combined (defined by the above ICDO3 codes and 9671, 9673, 9675, 9687, 9689, 9699, 9700, 9701, 9702, 9705, 9708, 9709, 9714, 9716, 9717, 9718, 9719, 9728, 9729, 9826, 9827, 9832, 9833, 9591, and 9727). As most studies did not recruit cases with HIV-associated lymphoid neoplasms these diagnoses were excluded.

Findings for the individual effects of BMI and cytokine SNPs on the risk of lymphoid neoplasms have been reported for the InterLymph studies (1,6–8). In all studies, adult height and weight were self-reported, with information on weight requested for one year (NCI-SEER, UCSF, Connecticut), two years (Mayo Clinic) or five years (UK) before diagnosis or interview date; or usual weight (SCALE, EpiLymph). BMI, calculated from weight in kilograms and height in metres, was classified according to World Health Organisation guidelines as: normal weight (18.5–<25kg m^{-2}); overweight (25–<30 kg m^{-2}) or; obese (≥30 kg m^{-2}); the 1% of the study population who were underweight (<18.5kg m^{-2}) were excluded from the analyses (22). BMI as a continuous variable was defined as per 5kg m^{-2} increase above 18.5 kg m^{-2}. Cytokine SNPs were tested using the Taqman™ platform (Applied Biosystems, Foster City, CA, USA), Pyrosequencing™, custom Illumina GoldenGate 1,536 SNP oligonucleotide pool (OPA) or iSelect (6–8,14). Twelve SNPs in nine candidate genes were investigated: 2q14, *IL1A* –889C→T (rs1800587; 4 studies, 2195 cases, 2082 controls), *IL1B* –511C→T (rs16944; 3 studies, 1843 cases, 1695 controls), and

IL1B –31C→T (rs1143627; 4 studies, 2188 cases, 2099 controls); in 2q14.2, *IL1RN* 9589A→T (rs454078; 3 studies, 1673 cases, 1598 controls); in 4q26-27, *IL2* 384T→G (rs2069762; 4 studies, 2185 cases, 2085 controls); in 7p21, *IL6* –174G→C (rs1800795; 4 studies, 2203 cases, 2095 controls) and *IL6* –597G→A (rs1800797; 3 studies, 1679 cases, 1591 controls); in 1q31-32, *IL10* –3575T→A (rs1800890; 9 studies, 5015 cases, 5061 controls) and *IL10* –1082A→G (rs1800896; 7 studies, 2844 cases, 3328 controls); in 6p21.3, *TNF*–308G→A (rs1800629; 9 studies, 4979 cases, 4752 controls) and *LTA*252A→G (rs909253; 9 studies, 5067 cases, 4879 controls); and in 16q21, *CARD15* Ex11-35→C (rs2066847; 7 studies, 4267 cases, 4092 controls). SNPs were modelled as dichotomous variables assuming dominant inheritance (heterozygous/homozygous variant versus homozygous wild type genotypes) as suggested by InterLymph analyses (6–8), to increase power and reduce the number of statistical tests. Due to potential ethnic differences in body fat and SNP distributions, analyses were restricted to persons who described themselves as of White European descent.

Statistical Analyses

Risk estimates were calculated using unconditional logistic regression adjusted for study, sex and age. Main and joint associations with BMI and each SNP on the risk of lymphoid neoplasms were estimated. Additive interactions between SNP and BMI were estimated by the relative excess risk due to interaction (RERI). When BMI was a categorical variable, the 95% confidence intervals (CI) for RERI were estimated using likelihood-based 95%CI (23). For BMI as a continuous variable, 10000 bootstrapping samples (without replacement) of the original sample size were taken from the dataset and the 95%CIs were the 2.5th and 97.5th centile of the bootstrap sampling distribution (24).

Analyses were repeated for DLBCL, FL and CLL/SLL, and all controls were used irrespective of the individual studies' matching techniques. Heterogeneity between study-specific risk estimates was considered present when a test for interaction between the variable of interest and study was statistically significant (p-value<0.05). Potential sources were investigated using sensitivity analyses by: study design (population- or hospital-based); diagnosis classification; participation rates; continent; proportions of cases and controls with SNP data; whether the controls' SNP data were in Hardy-Weinberg equilibrium; or where there was no relationship between obesity and the SNP among controls. All analyses were conducted using Stata 13.1.

Results

Data were received for a total of 5844 cases and 6167 controls. The majority of cases were diagnosed with mature B-cell neoplasms (90%), comprising DLBCL (28%), FL (23%), CLL/SLL (19%) and other B-cell subtypes (20%); 6% were T-cell in origin and 4% had no immunophenotype or subtype recorded. A higher proportion of cases were men (53%) and the median age at diagnosis was 60 years. Controls were more likely to be women, of younger age, and higher socioeconomic status than cases (Table 2).

Table 3 shows findings for the twelve cytokine polymorphisms among the subsets of subjects who had genotype data for each SNP as well as BMI data. Positive associations

were found with DLBCL for *TNF-308G>A* (odds ratio (OR)=1.24, 95% confidence interval (CI) 1.07–1.44), *IL10-1082A>G* (OR=1.14, 95% CI 1.00–1.31) and *CARD15 Ex11-35>C* (OR=1.25, 95%CI 1.10–1.56); with FL for the two *IL10* SNPs (*IL10-3575T>A*: OR=1.15, 95%CI 1.04–1.28; *IL10-1082A>G*: OR=1.10, 95%CI 1.05–1.15); and with CLL/SLL for *IL1RN 9589A>T* (OR=1.50, 95%CI 1.17–1.91). A few negative associations were also found for FL with *IL6 -597G>A* (OR=0.81, 95%CI 0.78–0.85) and *LTA 252A>G* (OR=0.93, 95%CI 0.87–0.99); and for CLL/SLL with *IL1B -511C>T* (OR=0.84, 95%CI 0.81–0.87). Table 4 shows findings between DLBCL, FL and CLL/SLL and being overweight or obese for the subsets of subjects with data for the five positively associated polymorphisms; findings for BMI in the subsets for the other seven polymorphisms were similar (data not shown). Risk estimates were increased for DLBCL among obese individuals compared to those of normal weight in subsets with *TNF-308G>A* (OR=1.33, 95% CI 1.02–1.73), *IL10-1082A>G* (OR=1.39, 95% CI 1.12–1.73) and *CARD15 Ex11-35>C* (OR=1.41, 95%CI 1.04–1.91) data. For FL, there was no evidence that being obese increased risk (OR=1.00, 95%CI 0.81–1.24; OR=1.13, 95%CI 0.91–1.40 in the *IL10-3575T>A* and *IL10-1082A>G* subsets for example); while for CLL/SLL, some decreased associations with obesity were found (OR=0.80, 95%CI 0.69–0.93 in the *IL10 -3575T>A* subset for example).

For DLBCL, the only subtype associated with obesity, tests for departure from additive interaction showed weak evidence for an additional effect of obesity and *TNF-308GA+AA* on DLBCL risk (P(interaction)=0.13); there was no evidence for the other two polymorphisms positively associated with this subtype (P(interaction)=0.77 and 0.85 for *IL10-1082A>G* and *CARD15 Ex11-35>C*, respectively). Table 5 shows joint associations of BMI and *TNF-308G>A* on DLBCL risk, with the relative excess risks due to interaction (RERI); for completeness, joint associations and RERIs of BMI and the other polymorphisms for all three subtypes are given in Supplementary Tables 1 and 2 for categorical and continuous BMI respectively. For DLBCL, risk estimates were increased among those who were overweight or obese irrespective of *TNF-308G>A* status (overweight & GG: OR=1.21, 95%CI 1.02–1.44; overweight & GA+AA: OR=1.31, 95%CI 1.00–1.71; obese & GG: OR=1.25, 95%CI 1.00–1.56). However, being both obese and having the *TNF-308A* allele almost doubled the risk estimate compared to persons of normal weight who did not carry the A allele (OR=1.93 95%CI 1.27–2.94); an additional risk from being obese and having *TNF-308A* variant rather than having either risk factor alone was suggested (RERI=0.41, 95%CI −0.05, 0.84). Similarly, increased trends with 5kg m^{-2} increase in BMI above 18.5kg m^{-2} were seen in homozygous wild types and variant TNF-308A carriers (OR=1.14, 95%CI 1.07–1.22; OR=1.19, 95%CI 1.12–1.27 respectively). The corresponding RERI of 0.05 (95%CI −0.005–0.08) suggests that with every 5kg m^{-2} rise in BMI, the risk of DLBCL is 0.05 more than if there was no interaction.

Joint associations of BMI and *TNF-308G>A* genotype on DLBCL risk were not consistent across studies (P(heterogeneity)=0.02). Associations were similar among North American studies, with evidence of additive interaction (RERI=1.27, 95%CI 0.48,2.08); but not among European studies (RERI=−0.25, 95%CI −0.84,0.28) (Table 6). Heterogeneity was present among studies that were population-based; which used the ICDO3 disease classification; where participation rates were 70% or more; where 90% or more of subjects were

genotyped; where control distributions of *TNF* genotypes were in HWE; or where BMI and *TNF-308G>A* genotypes were not correlated among controls. In these groupings, the risk estimates of being obese and having *TNF-308GA+AA* genotype tended to be similar, and RERIs were all above zero, although most were not statistically significant.

Discussion

This InterLymph analysis of the joint associations of BMI and cytokine polymorphisms on the risk of the three most common lymphoid neoplasms found some evidence of interaction between obesity and *TNF-308G>A* (rs1800629). For DLBCL, the risk was greatest among those who were obese and carried the *TNF-308A* allele, although risk was also increased among the overweight regardless of *TNF* status. The associations showed some variation between studies, but these differences were not explained by study design, disease classification or other factors. On the other hand, being obese and carrying *TNF-308A* did not increase the risk of either FL or CLL/SLL. Besides *TNF-308G>A*, other cytokine SNPs in *IL1A* (rs1800587), *IL1B* (rs16944, rs1143627), *IL1RN* (rs454078), *IL2* (rs2069762), *IL6* (rs1800795, rs1800797), *IL10* (rs1800890, rs1800896), *LTA* (rs909253), and *CARD15* (rs2066847) showed little evidence of altering the NHL risk associated with being overweight.

Since publication of the InterLymph pooled analysis of BMI, where we reported that obesity increased DLBCL risk (1), several studies including cohorts have also found this relationship (25–29) while others have not (11,30–36). In summarising published data for DLBCL and obesity, two meta-analyses have noted an increased risk (3,4), the latest including all but the most recent publications (27,28). Unfortunately, however, several studies which reported no association with total NHL did not stratify their data by subtype (32,37–39). To further explore the mechanisms underlying the relationship between obesity and lymphoma, chronic inflammation involving cytokine production is one possible pathway that has been investigated mostly by examining SNPs (9–11), although the functional roles for some are not yet conclusive (40). One study measured pre-diagnosis serum levels of cytokines and found no association between TNF levels and NHL among either normal or over- weight persons (9). When examining SNPs in *TNF*, Wang and colleagues noted an excess risk of DLBCL among obese individuals carrying the *TNF-308A* allele and, although Chen *et al* did not report joint associations, a similar finding among overweight women is suggested (crude OR=1.8, 95%CI 1.0–3.2) (10,11). To our knowledge, these are the only studies to have investigated cytokine SNPs in relation to the effect obesity may have on lymphoma risk, and both are included in this pooled analysis.

TNF has been implicated in the relationship between obesity and several other cancers including breast, endometrium and gastrointestinal (41–43); the promotion of tumour cell proliferation through activation of nuclear factor κB (NFκB) being suggested as the most likely explanation (44). In obesity, B cells, T cells and macrophages infiltrate the expanding adipose tissue, and not only lead to, but also maintain, a chronic inflammatory state (5). The macrophages secrete most of the TNF produced by adipose tissue, which escapes into circulation to bind to and activate its receptor TNFR, which is expressed in all human tissues (5,41). TNF activates IL6 in adipose tissue and downstream of both cytokines are the NFκB

and STAT3 cycles. These pathways have important roles in lymphocyte development, function and survival, and deregulation of these cycles are seen in lymphoid malignancies including DLBCL, the most common aggressive subtype examined here (26). Obesity-related lymphomagenesis is likely to be complex involving the actions of additional pro-inflammatory cytokines and immuno-modulatory mediators that trigger downstream targets that promote the clonal expansion and transformation of B cells with premalignant lesions. Further studies will be needed to investigate possible disease mechanisms.

When assessing gene-environment interactions, differential misclassification can bias the interaction estimate in either direction (45). Our data may not be free from differential case-control participation and reporting. Among controls, obesity-related health problems may have influenced their participation and for cases, although rapid ascertainment techniques were employed, those with poor survival, which may be related to different degrees of adiposity (46), could have been missed. Our anthropometric data were self-reported and BMI could be biased towards “normal” weight since respondents tend to overestimate their height and underestimate their weight to varying degrees dependent on their gender and age (47). Cases’ responses could also have been influenced by weight loss associated with lymphoma, although several studies attempted to compensate for this by requesting weight at a year or more before diagnosis. The effect of participation bias on our finding of an interaction will be limited if obesity and *TNF-308G>A* are associated in the general population. *TNF-308G>A* SNP has been suggested to be related- albeit weakly - to obesity, but the mechanism for *TNF* gene involvement in obesity pathogenesis is unclear (48). If there is an association, persons carrying the variant allele may be under- (or over-) represented in our data if body fatness is related to participation, or the stratum-specific frequencies on gene and BMI category could be inaccurate, biasing the interaction estimate in either direction. Among our controls *TNF* genotype and BMI overall were not correlated in all but two of our studies (NCI-SEER, EpiLymph-Spain); the removal of these did not alter our findings.

Strengths of our study include its large sample size, giving the potential to examine interactions and explore differences in interactions among the most common lymphoid neoplasms. Obesity prevalence varies across countries, which could relate differently to subjects’ participation and responses in the studies included. Most studies had not published on this topic before, and while data were a subset of studies and subjects included in the main effects analyses, the risk estimates for BMI and SNPs were consistent with those published previously (1,6–8). A reduced risk of CLL/SLL with obesity was found in some subsets of data, which could relate to disease-related weight loss; but in larger InterLymph datasets, no obesity associations for CLL/SLL have been reported (1). Other limitations are the low power to assess interactions in less common lymphoid neoplasms, and some SNPs which were tested in only a few studies. Indeed, statistically significant interactions were found with SNPs genotyped in all nine studies, and others with fewer may have shown an effect had we had more data. Many other candidate cytokine SNPs were not associated with lymphoid neoplasms, and so it is not surprising that no joint association was found between obesity and these SNPs. BMI in this analysis related to weight at older age and there was no evidence that associations were different among those aged under, or over, 65 years; data on

BMI in young adulthood- which has been associated with DLBCL (2,31)- were too sparse. As for generalizability, our findings may not translate to all populations as our subjects were Caucasian and resident in developed nations.. Furthermore, the body mass index was developed to estimate body fat in Caucasians of working age and so may not be applicable to other groups; no other indicators such as waist-hip ratio were available. There is certainly variation in obesity rates worldwide (49), and also the distribution of *TNF-308G>A* genotypes and those of the other SNPs studied here differ between populations too (50).

In conclusion, we found some evidence of interaction between *TNF-308G>A* and BMI on the risk of DLBCL. The increased risk among persons carrying the variant *TNF-308A* allele and being obese was not necessarily consistent across studies however, and the possibility that differential biases affected the findings cannot be ruled out. One way to potentially reduce these biases is to examine gene-environment associations in large cohort studies using more specific measures of adiposity such as total body fat, and obtaining data on circulating levels of TNF and other cytokines. Furthermore, within InterLymph, genome-wide association scans are now completed for more studies than included here (51), and findings from these may identify other adipose tissue-related cytokines and adipokines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of case-control studies included in the pooled analysis.

Study	Location	Years of Diagnosis	Age Range	Cases (N=5844)		Controls (N=6167)		
				N	Participation (%)	Source	N	Participation (%)
NCI-SEER(12)	Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington, USA	1998–2001	20–70	895	76	<65 years Random digit dialling; 65+ years random selection from Centers for Medicare and Medicaid Services, stratified by study area, age, sex and race	686	52
Mayo Clinic Phases 1–3(13,14)	Iowa, Wisconsin, Minnesota, USA	2002–2008	18+	887	69	Frequency matched by age, sex and county of residence	1046	69
UCSF(15)	San Francisco, USA	1988–1995	21–74	309	72	Random digit dialling, frequency matched by age, sex, and county of residence	685	78
Connecticut(16)	Connecticut USA	1995–2001	21–84 women only	483	72	Women only: <65 years Random Digit Dialling; 65+ years random selection from Centers for Medicare and Medicaid Services. Frequency matched within 5 years of age	553	RDD:69; CMMS:47
UK(17)	Yorkshire, Lancashire, South Lakeland and parts of Southwest England	1998–2003	16–69	626	70	Random selection from general practice lists, individually matched by age, sex and region of residence	784	69
SCALE Denmark(18)	Denmark	2000–2002	18–74	768	81	Random selection from population register, frequency matched by sex and age	745	71
SCALE Sweden(18)	Sweden	2000–2002	18–74	1528	81	Random selection from population register, frequency matched by sex and age	1116	71
EpiLymph France(19)	Amiens, Dijon and Montpellier	2000–2003	18–80	85	91	Hospital controls matched by age (±5 years), sex and study region	129	74
EpiLymph Spain(20)	Barcelona, Tortosa, Reus and Madrid	1998–2002	18–80	263	82	Hospital controls matched by age (±5 years), sex and study region	423	96

Table 2

Demographics of cases and controls.

	Cases N(%)	Controls N(%)
Total	*5844(100)*	*6167(100)*
Diagnosis		
B-cell	*5241(90)*	-
DLBCL	1643(28)	-
Follicular	1344(23)	-
CLL/SLL	1089(19)	
Other	1165(20)	-
T-cell	*342(6)*	-
Not Otherwise Specified	*261(3)*	-
Sex		
Male	3088(53)	3101(50)
Female	2756(47)	3066(50)
Age		
<46	803(14)	1128(18)
46–55	1319(23)	1236(20)
56–65	1824(31)	1710(28)
>65	1898(32)	2093(34)
Socioeconomic Status		
Low	2130(36)	2045(33)
Medium	1825(31)	1945(32)
High	1860(32)	2145(35)
Not Known	29(0.5)	32(0.5)
BMI(kg m^{-2})		
Underweight: <18.5	57(1)	75(1)
Normal weight: 18.5–<25	2573(44)	2851(46)
Overweight: 25–<30	2214(38)	2275(37)
Obese: ≥30	1000(17)	966(16)

Table 3

Associations with cytokine polymorphisms among cases and controls with body mass index data.

	DLBCL[a]			FL[a]			CLL/SLL[a]			Lymphoid Neoplasms[a]		
	Case/Control	**OR[b]**	**95%CI**	**Case/Control**	**OR[b]**	**95%CI**	**Case/Control**	**OR[b]**	**95%CI**	**Case/Control**	**OR[b]**	**95%CI**
TNF -308G→A (rs1800629)												
no of studies=9[c]	*1477/4752*	*χ^2=12.9*	*p_{het}=0.11*	*1176/4752*	*χ^2=4.22*	*p=0.84*	*875/3576*	*χ^2=13.5*	*p_{het}=0.04*	*4979/4752*	*χ^2=11.3*	*p_{het}=0.19*
GG	951/3322	1	ref	827/3322	1	ref	594/2525	1	ref	3319/3322	1	ref
GA/AA	513/1371	1.24	1.07–1.44	344/1371	0.95	0.86–1.06	271/1000	1.08	0.87–1.34	1616/1371	1.14	1.02–1.27
LTA 252A→G (rs909253)												
no of studies=9[c]	*1510/4879*	*χ^2=19.3*	*p_{het} =0.01*	*1184/4879*	*χ^2=2.11*	*p_{het} =0.98*	*888/3694*	*χ^2=10.2*	*p_{het} =0.12*	*5067/4879*	*χ^2=11.0*	*p_{het} =0.20*
AA	620/2201	1	ref	544/2021	1	ref	371/1701	1	ref	2161/2201	1	ref
AG/GG	877/2617	1.15	0.95–1.40	634/2617	0.93	0.87–0.99	507/1941	1.14	0.99–1.31	2860/2617	1.08	0.98–1.18
IL10 –3575T→A (rs1800890)												
no of studies=9[c]	*1515/5061*	*χ^2=19.5*	*p_{het} =0.01*	*1160/5061*	*χ^2=6.57*	*p_{het} =0.58*	*883/3895*	*χ^2=5.61*	*p_{het} =0.47*	*5015/5061*	*χ^2=14.6*	*p_{het} =0.07*
TT	430/1559	1	ref	324/1559	1	ref	231/1136	1	ref	1375/1559	1	ref
TA/AA	1072/3442	1.08	0.87–1.35	830/3442	1.15	1.04–1.28	642/2708	0.91	0.80–1.04	3595/3442	1.07	0.95–1.22
IL10 –1082A→G (rs1800896)												
no of studies=7[c]	*948/3328*	*χ^2=4.25*	*p_{het} =0.64*	*779/3328*	*χ^2=2.00*	*p_{het} =0.92*	*340/2161*	*χ^2=5.94*	*p_{het} =0.20*	*2844/3328*	*χ^2=4.66*	*p_{het} =0.59*
AA	240/944	1	ref	199/944	1	ref	101/631	1	ref	744/944	1	ref
AG/GG	702/2339	1.14	1.00–1.31	576/2339	1.10	1.05–1.15	236/1494	0.98	0.72–1.35	2077/2339	1.11	1.03–1.20
CARD15 Ex11–35→C (rs2066847)												
no of studies=6[c]	*1261/4092*	*χ^2=3.26*	*p_{het} =0.66*	*972/4092*	*χ^2=12.6*	*p_{het} =0.03*	*735/2645*	*χ^2=2.65*	*p_{het} =0.45*	*4267/4092*	*χ^2=3.71*	*p_{het} =0.59*
−−	1199/3098	1	ref	937/3098	1	ref	703/2530	1	ref	4081/3098	1	ref
−+/++	51/138	1.25	1.01–1.56	32/138	1.06	0.48–2.36	23/83	1.28	0.79–2.08	147/138	1.17	0.92–1.49
IL1A –889C→T (rs1800587)												
no of studies=4[c]	*778/2082*	*χ^2=1.49*	*p_{het} =0.68*	*634/2082*	*χ^2=2.63*	*p_{het} =0.45*	*234/1601*	*χ^2=2.77*	*p_{het} =0.25*	*2195/2082*	*χ^2=3.83*	*p_{het} =0.28*
CC	396/998	1	ref	311/998	1	ref	108/770	1	ref	1082/998	1	ref
CT/TT	377/1054	0.90	0.80–1.00	320/1054	0.96	0.81–1.13	124/808	1.09	0.80–1.48	1096/1054	0.95	0.84–1.08
IL1B –31C→T (rs1143627)												
no of studies=4[c]	*769/2099*	*χ^2=5.99*	*p_{het} =0.11*	*633/2099*	*χ^2=6.28*	*p_{het} =0.10*	*232/1621*	*χ^2=2.65*	*p_{het} =0.27*	*2188/2099*	*χ^2=5.08*	*p_{het} =0.17*

	DLBCL[a]			FL[a]			CLL/SLL[a]			Lymphoid Neoplasms[a]		
	Case/Control	**OR[b]**	**95%CI**	**Case/Control**	**OR[b]**	**95%CI**	**Case/Control**	**OR[b]**	**95%CI**	**Case/Control**	**OR[b]**	**95%CI**
CC	340/922	1	ref	284/922	1	ref	107/730	1	ref	988/922	1	ref
CT/TT	423/1147	0.97	0.75–1.26	346/1147	0.96	0.75–1.23	123/868	0.98	0.70–1.37	1182/1147	0.96	0.83–1.11
IL2 –384T→G (rs2069762)												
no of studies=4[c]	*770/2085*	*χ^2=4.83*	*p_{het} =0.19*	*635/2085*	*χ^2=2.40*	*p_{het} =0.49*	*232/1604*	*χ^2=2.30*	*p_{het} =0.32*	*2185/2085*	*χ^2=4.70*	*p_{het} =0.20*
TT	388/1007	1	ref	309/1007	1	ref	112/775	1	ref	1062/1007	1	ref
TG/GG	376/1048	0.93	0.79–1.09	323/1048	0.99	0.85–1.15	118/806	1.03	0.80–1.33	1105/1048	1.00	0.86–1.16
IL6 –174G→C (rs1800795)												
no of studies=4[c]	*772/2095*	*χ^2=3.77*	*p_{het} =0.29*	*640/2095*	*χ^2=4.70*	*p_{het} =0.20*	*234/1620*	*χ^2=2.71*	*p_{het} =0.26*	*2203/2095*	*χ^2=2.13*	*p_{het} =0.55*
GG	271/703	1	ref	222/703	1	ref	81/541	1	ref	777/703	1	ref
GC/CC	495/1362	0.94	0.79–1.12	415/1362	0.94	0.73–1.21	151/1056	0.92	0.66–1.22	1408/1362	0.93	0.83–1.03
IL1B –511C→T (rs16994)												
no of studies=3[c]	*708/1695*	*χ^2=6.77*	*p_{het} =0.03*	*542/1695*	*χ^2=2.99*	*p_{het} =0.22*	*136/1217*	*χ^2=0.01*	*p_{het} =0.92*	*1843/1695*	*χ^2=3.96*	*p_{het} =0.14*
CC	311/733	1	ref	247/733	1	ref	67/543	1	ref	832/733	1	ref
CT/TT	392/934	0.98	0.71–1.35	292/934	0.92	0.74–1.14	68/653	0.84	0.59–1.20	996/934	0.94	0.79–1.12
IL1RN 9589A→T (rs454078)												
no of studies=3[c]	*478/1598*	*χ^2=5.75*	*p_{het} =0.06*	*422/1598*	*χ^2=2.78*	*p_{het} =0.25*	*231/1598*	*χ^2=2.07*	*p_{het} =0.36*	*1673/1598*	*χ^2=3.98*	*p_{het} =0.14*
AA	250/885	1	ref	210/885	1	ref	105/885	1	ref	849/885	1	ref
AT/TT	224/691	1.16	0.88–1.53	209/691	1.26	0.96–1.65	124/691	1.50	1.17–1.91	808/691	1.22	1.01–1.48
IL6 –597G→A (rs1800797)												
no of studies=3[c]	*488/1591*	*χ^2=3.99*	*p_{het} =0.14*	*421/1591*	*χ^2=0.08*	*p_{het} =0.96*	*233/1591*	*χ^2=2.17*	*p_{het} =0.34*	*1679/1591*	*χ^2=0.31*	*p_{het} =0.86*
GG	169/536	1	ref	160/536	1	ref	85/536	1	ref	615/535	1	ref
GA/AA	315/1031	0.95	0.71–1.28	258/1031	0.81	0.78–0.85	146/1031	0.87	0.67–1.12	1048/1031	0.87	0.82–0.93

[a] DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL/SLL: chronic lymphocytic leukaemia/small lymphocytic lymphoma.

[b] Odds ratios (OR) and 95% confidence intervals (CI) estimated using logistic regression adjusted for sex, age and study.

[c] Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the cytokine and study variables with the basic model which adjusted for study. For FL, EpiLymph- France and Spain were considered together due to small numbers of cases in some strata. Fewer studies had data for CLL/SLL (7 studies with TNF-308G>A, LTA252A>G or IL10-3575T>A data; 5 studies with IL10-1082A>G or CARD15 Ex11–35→C data; 3 studies with IL1A-889C>T, IL1B-31C>T, IL2-384T>G or IL6-174G>C data; and 2 studies with IL1B-511C>T data).

Table 4

Associations with body mass index among cases and controls where an association with cytokine polymorphism.

	DLBCL[b]			FL[b]			CLL/SLL[b]			Lymphoid Neoplasms[b]		
BMI[a]	**Case/Control**	**OR[c]**	**95%CI**	**Case/Control**	**OR[c]**	**95%CI**	**Case/Control**	**OR[c]**	**95%CI**	**Case/Control**	**OR[c]**	**95%CI**
TNF -308G→A (rs1800629)												
no of studies=9[d]	*1477/4752*	*χ^2=31.2*	*p_{het}=0.01*	*1176/4752*	*χ^2=11.6*	*p_{het}=0.77*	*875/3576*	*χ^2=6.79*	*p_{het}=0.87*	*4979/4752*	*χ^2=30.1*	*p_{het}=0.02*
Normal	650/2275	1	ref	567/2275	1	ref	396/1580	1	ref	2262/2275	1	ref
Overweight	548/1689	1.14	0.91–1.43	422/1689	1.05	0.92–1.20	344/1310	0.90	0.75–1.10	1862/1689	1.05	0.90–1.21
Obese	266/729	1.33	1.02–1.73	182/729	1.05	0.87–1.26	125/635	0.80	0.67–0.96	811/729	1.08	0.90–1.30
Per 5kg m^{-2}		1.16	1.09–1.23		1.02	0.95–1.10		0.93	0.85–1.02		1.05	1.01–1.10
IL10 –3575T→A (rs1800890)												
no of studies=9[d]	*1515/5061*	*χ^2=29.9*	*p_{het}=0.02*	*1160/5061*	*χ^2=14.0*	*p_{het}=0.60*	*883/3895*	*χ^2=8.02*	*p_{het}=0.78*	*5015/5061*	*χ^2=30.2*	*p_{het}=0.02*
Normal	660/2406	1	ref	565/2406	1	ref	399/1717	1	ref	2281/2406	1	ref
Overweight	575/1822	1.15	0.93–1.42	413/1822	1.03	0.89–1.19	347/1449	0.89	0.72–1.11	1882/1822	1.02	0.87–1.20
Obese	267/773	1.29	0.98–1.69	176/773	1.00	0.81–1.24	127/678	0.80	0.69–0.93	807/773	1.04	0.86–1.27
Per 5kg m^{-2}		1.15	1.08–1.22		1.01	0.94–1.09		0.92	0.84–1.01		1.04	0.99–1.09
IL10 –1082A→G (rs1800896)												
no of studies=7[d]	*948/3328*	*χ^2=19.7*	*p_{het}=0.07*	*779/3328*	*χ^2=8.57*	*p_{het}=0.74*	*340/2161*	*χ^2=2.28*	*p_{het}=0.97*	*2844/3328*	*χ^2=16.0*	*p_{het}=0.19*
Normal	404/1568	1	ref	362/1568	1	ref	132/878	1	ref	1215/1568	1	ref
Overweight	343/1151	1.20	1.05–1.38	273/1151	1.09	0.93–1.28	140/778	0.96	0.76–1.20	1040/1151	1.10	1.00–1.21
Obese	195/564	1.39	1.12–1.73	140/564	1.13	0.91–1.40	65/469	0.75	0.63–0.90	566/564	1.15	1.00–1.33
Per 5kg m^{-2}		1.15	1.07–1.24		1.04	0.96–1.13		0.89	0.79–1.01		1.06	1.01–1.12
CARD15 Ex11–35→C (rs2066847)												
no of studies=6[d]	*1261/4092*	*χ^2=19.5*	*p_{het}=0.03*	*972/4092*	*χ^2=7.43*	*p_{het}=0.68*	*735/2645*	*χ^2=6.46*	*p_{het}=0.37*	*4267/4092*	*χ^2=23.5*	*p_{het}<0.01*
Normal	553/2005	1	ref	486/2005	1	ref	345/1165	1	ref	1983/2005	1	ref
Overweight	469/1483	1.10	0.85–1.42	356/1483	1.03	0.89–1.18	285/1010	0.85	0.67–1.08	1614/1483	1.01	0.85–1.20
Obese	228/558	1.41	1.04–1.91	127/558	0.94	0.78–1.14	96/438	0.79	0.61–1.01	631/558	1.04	0.81–1.34
Per 5kg m^{-2}		1.19	1.11–1.27		0.99	0.91–1.08		0.91	0.82–1.02		1.04	0.99–1.09
IL1RN 9589A→T (rs454078)												
no of studies=3[d]	*478/1598*	*χ^2=3.99*	*p_{het}=0.41*	*422/1598*	*χ^2=2.94*	*p_{het}=0.57*	*231/1598*	*χ^2=2.06*	*p_{het}=0.72*	*1673/1598*	*χ^2=1.37*	*p_{het}=0.85*

	DLBCL[b]			FL[b]			CLL/SLL[b]			Lymphoid Neoplasms[b]		
BMI[a]	**Case/Control**	**OR[c]**	**95%CI**	**Case/Control**	**OR[c]**	**95%CI**	**Case/Control**	**OR[c]**	**95%CI**	**Case/Control**	**OR[c]**	**95%CI**
Normal	163/650	1	ref	175/650	1	ref	88/650	1	ref	628/650	1	ref
Overweight	186/575	1.30	1.25–1.35	143/575	0.94	0.78–1.13	94/575	0.97	0.64–1.46	625/575	1.09	0.98–1.22
Obese	125/351	1.43	0.99–2.05	101/351	1.05	0.79–1.41	47/351	0.79	0.61–1.03	404/351	1.16	1.12–1.19
Per 5kg m^{-2}		1.16	1.06–1.28		1.01	0.91–1.12		0.93	0.80–1.07		1.07	1.00–1.14

[a] BMI: body mass index, Normal weight=18.5–<25kg m^{-2}, Overweight=25–<30kg m^{-2}, Obese=≥30kg m^{-2}.

[b] DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL/SLL: chronic lymphocytic leukaemia/small lymphocytic lymphoma.

[c] Odds ratios (OR) and 95% confidence intervals (CI) estimated using logistic regression adjusted for sex, age and study.

[d] Tests for heterogeneity between studieswere conducted using the likelihood ratio test to compare the model with an interaction term between the BMI and study variables with the basic model which adjusted for study. For FL, EpiLymph- France and Spain were considered together due to small numbers of cases in some strata. Fewer studies had data for CLL/SLL (7 studies with TNF-308G>A or IL10-3575T>A data; and 5 studies with IL10-1082A>G or CARD15 Ex11–35→C data).

Table 5

Joint associations and relative excess risks due to interaction between body mass index and tumour necrosis factor -308G>A (rs1800629) for diffuse large B-cell lymphoma.

	*TNF -308*GG		*TNF -308*GA/AA		
BMI[a]	**Cases/Controls**	**OR(95% CI)**[b]	**Cases/Controls**	**OR(95% CI)**[b]	***RERI(95%CI)***[c]
Normal	412/1591	1(ref)	238/684	1.27(1.07–1.52)	-
Overweight	372/1201	1.21(1.02–1.44)	176/488	1.31(1.00–1.71)	−0.18(−0.47,0.10)
Obese	167/530	1.25(1.00–1.56)	99/199	1.93(1.27–2.94)	0.41(−0.05,0.84)
		χ^2=59.9, p_{het}=0.02[d]			χ^2=4.10, pint=0.13[e]
Per 5kg m^{-2}		1.14(1.07–1.22)		1.19(1.12–1.27)	0.05(−0.005,0.08)

[a] BMI: body mass index, Normal weight=18.5–<25kg m^{-2}, Overweight=25–<30kg m^{-2}, Obese=≥30kg m^{-2}.

[b] Odds ratios (OR) and 95% confidence intervals (CI) estimated using logistic regression adjusted for sex, age and study.

[c] Relative Excess Risk due to Interaction (RERI) estimated using linear odds ratio regression adjusted for sex, age and study and its 95% CI for categorical BMI were likelihood-based, derived using maximum likelihood estimation; or by bootstrapping percentile method for continuous BMI.

[d] Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the joint effect and study variables with the basic model which adjusted for study

[e] Tests for departure from additive interaction between BMI and TNF were conducted using the likelihood ratio test on linear odds ratio model.

Table 6

Sensitivity analyses by study design factors on overall risk estimates and relative excess risks due to interaction for diffuse large B-cell lymphoma associated with being obese and having tumor necrosis factor -308A genotype (rs1800629).

	Studies	Study Heterogeneity[a]	Normal GA +AA[b] OR (95%CI)[c]	Obese GG[b] OR (95%CI)[c]	Obese GA+AA[b] OR(95%CI)[c]	Departure from additive interaction[d]	Obese GA+AA[b] RERI(95%CI)[e]
Continent							
North America	NCI-SEER, Mayo, UCSF1, Connecticut	χ^2=12.0, p_{het}=0.68	1.25(0.91–1.70)	1.19(0.88–1.62)	2.71(1.84–4.01)	χ^2=7.56, pint=0.02	1.27(0.48,2.08)
Europe	UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France, EpiLymph-Spain	χ^2=38.1, p_{het}=0.01	1.29(1.02–1.63)	1.37(1.01–1.85)	1.40(0.95–2.07)	χ^2=2.45, pint=0.29	−0.25(−0.84,0.28)
Study design							
Population-based	NCI-SEER, UCSF1, Connecticut, UK, SCALE- Denmark, SCALE-Sweden	χ^2=39.7, p_{het}=0.03	1.25(1.03–1.52)	1.29(1.00–1.65)	2.05(1.27–3.32)	χ^2=5.31, pint=0.07	0.51(0.004,1.00)
Clinic/Hospital-based	Mayo, EpiLymph-France, EpiLymph-Spain	χ^2=16.0, p_{het}=0.10	1.62(1.23–2.14)	1.06(0.71–1.58)	1.34(0.54–3.35)	χ^2=0.33, pint=0.85	−0.33(−1.79,1.13)
Diagnosis Classification							
ICDO3	NCI-SEER, Mayo, UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France, Epilymph- Spain	χ^2=47.1, p_{het}=0.02	1.29(1.03–1.62)	1.34(1.07–1.69)	1.84(1.13–3.00)	χ^2=2.19, pint=0.33	0.20(−0.31,0.68)
Other	UCSF1, Connecticut	χ^2=8.02, p_{het}=0.16	1.21(1.06–1.38)	0.83(0.72–0.96)	2.66(0.59–12.1)	χ^2=5.24, pint=0.07	1.62(0.41,2.97)
Participation Rate							
≥70%	UCSF1, SCALE-Denmark, SCALE-Sweden, EpiLymph-France, EpiLymph-Spain	χ^2=44.1, p_{het}<0.01	1.21(0.87–1.69)	1.14(0.81–1.60)	1.56(0.80–3.02)	χ^2=0.43, pint=0.81	0.20(−0.41,0.78)
<70%	NCI-SEER, Mayo, Connecticut, UK	χ^2=14.9, p_{het}=0.46	1.36(1.26–1.46)	1.34(1.00–1.80)	2.32(1.52–3.56)	χ^2=4.77, pint=0.09	0.63(−0.08,1.30)
Proportion of study subjects with TNF genotype							
≥90%	NCI-SEER, UCSF1, Connecticut, SCALE-Denmark, EpiLymph-France, EpiLymph-Spain	χ^2=38.9, p_{het}=0.04	1.12(0.89–1.42)	1.24(0.95–1.62)	2.36(1.47–3.77)	χ^2=6.84, pint=0.03	1.00(0.37,1.64)
<90%	Mayo, UK, SCALE-Sweden	χ^2=7.10, p_{het}=0.72	1.46(1.42–1.51)	1.30(0.80–2.13)	1.45(0.89–2.36)	χ^2=7.08, pint=0.03[f]	−0.32(−1.04,0.30)
Controls' TNF genotypes in Hardy-Weinberg Equilibrium							
Yes	NCI-SEER, Mayo, Connecticut, UK, SCALE- Denmark, SCALE-Sweden, EpiLymph-France	χ^2=43.4, p_{het}=0.05	1.28(1.05–1.58)	1.26(0.98–1.61)	1.88(1.22–2.90)	χ^2=4.19, pint=0.12	0.34(−0.15,0.79)
No	UCSF1, EpiLymph-Spain	χ^2=15.4, p_{het}<0.01	1.21(0.95–1.53)	1.20(0.84–1.73)	2.37(0.26–21.8)	χ^2=1.59, pint=0.45	0.96(−0.50,2.55)
BMI-TNF association among Controls							

	Studies	Study Heterogeneity[a]	Normal GA +AA[b] OR (95%CI)[c]	Obese GG[b] OR (95%CI)[c]	Obese GA+AA[b] OR(95%CI)[c]	Departure from additive interaction[d]	Obese GA+AA[b] RERI(9
No	Mayo, UCSF1, Connecticut, UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France	χ^2=44.5, p_{het}=0.04	1.27(1.04–1.56)	1.17(0.85–1.62)	1.76(1.16–2.67)	χ^2=4.60, pint=0.10	0.31(−0.20,0.80)
Yes	NCI-SEER, EpiLymph-Spain	χ^2=8.21, p_{het}=0.15	1.33(1.20–1.48)	1.43(1.40–1.46)	2.60(1.09–6.22)	χ^2=1.65, pint=0.44	0.84(−0.32,1.93)

[a] Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the joint association and study variables with the basic model which adjusted for study.

[b] Normal weight=18.5–<25kg m^{-2}, Obese=≥30kg m^{-2}; GG and GA+AA are *TNF-308G>A* genotypes where G is considered wild type, and A the variant, allele.

[c] Odds ratios (OR) and 95% confidence intervals (CI) estimated using logistic regression adjusted for sex, age and study where referent group was normal weight and *TNF-308GG* genotype. ORs shown for Normal GA+AA and Obese GG to aid interpretation of relative excess risk due to interaction

[d] Tests for departure from additive interaction between BMI and *TNF* were conducted using the likelihood ratio test on linear odds ratio model.

[e] Relative Excess Risk due to Interaction (RERI) estimated using linear odds ratio regression adjusted for sex, age and study and its likelihood-based 95% CI were derived using maximum likelihood estimation.

[f] Statistically significant departure from additive interaction due to RERI for Overweight (25–<30kg m^{-2}) & GA+AA.

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